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ORIGINAL REPORT

Evaluation of a Web-Based Cognitive Rehabilitation Program in Cancer Survivors Reporting Cognitive Symptoms After Chemotherapy

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A B S T R A C T

Purpose

Cognitive impairment is reported frequently by cancer survivors. There are no proven treatments. We evaluated a cognitive rehabilitation program (Insight) and compared it with standard care in cancer survivors self-reporting cognitive symptoms.

Patients and Methods

We recruited adult cancer survivors with a primary malignancy (excluding central nervous system malignancies) who had completed three or more cycles of adjuvant chemotherapy in the previous 6 to 60 months and reported persistent cognitive symptoms. All participants received a 30-minute telephone consultation and were then randomly assigned to the 15-week, home-based intervention or to standard care. Primary outcome was self-reported cognitive function (Functional Assessment of Cancer Therapy Cognitive Function [FACT-COG] perceived cognitive impairment [PCI] subscale): difference between groups after intervention (T2) and 6 months later (T3).

Results

A total of 242 participants were randomly assigned: median age, 53 years; 95% female. The primary outcome of difference in FACT-COG PCI was significant, with less PCI in the intervention group at T2 ($P < .001$). This difference was sustained at T3 ($P < .001$). At T2, there was a significant difference in all FACT-COG subscales, favoring the intervention. Neuropsychological results were not significantly different between the groups at T2 or T3. There were significantly lower levels of anxiety/depression and fatigue in the intervention group at T2. There were significant improvements in stress in the intervention group at both time points. There was no significant difference in quality of life between the groups at T2, but the intervention group had better quality of life at T3.

Conclusion

The intervention, Insight, led to improvements in cognitive symptoms compared with standard care. To our knowledge, this is the first large randomized controlled trial showing an improvement in self-reported cognitive function in cancer survivors, indicating that this intervention is a feasible treatment.

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INTRODUCTION

Up to 70% of patients with cancer report cognitive symptoms after chemotherapy.[1] Several studies have shown that self-reported cognitive impairment is associated with increased anxiety, depression, and fatigue and poorer quality of life (QOL).[2] However, most have found a weak association between cognitive symptoms and objective cognitive impairment on neuropsychological testing.[3] The cause remains poorly understood, and there are no proven treatments.[4]

Cognitive rehabilitation refers to behaviorally orientated interventions designed to improve performance in cognitive and functional domains, thereby enhancing an individual's functional capacity. These interventions have been shown to improve cognitive function, goal attainment behavior, memory problem solving, and psychosocial functioning in patients with traumatic brain injury.[5] Retraining programs work best in those with mild cognitive impairment who are sufficiently functional to engage in the program and apply the training to real-world demands.[6] These characteristics are often seen in cancer survivors.

Evaluation of cognitive rehabilitation programs in patients with cancer has been limited. Ferguson et al[7] evaluated a cognitive-behavioral treatment in

ASSOCIATED CONTENT

Appendix
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a single-arm pilot study in 29 breast cancer survivors reporting cognitive symptoms 8 years after chemotherapy. Participants had improvements in cognitive symptoms, neuropsychological performance, and QOL after the intervention, which were sustained at 6 months. In a follow-up wait-list control study, the researchers found improved verbal memory and QOL after the intervention.[8]

A wait-list randomized controlled trial (RCT) by Kesler et al[9] of an online cognitive training program in 41 patients with breast cancer an average of 6 years after treatment suggested efficacy of cognitive training with improvement in cognitive flexibility, verbal fluency, and processing speed. There were also improvements in self-reported planning, organization, and task monitoring.

The Web-based cognitive rehabilitation program, Insight, and its companion program have demonstrated benefits in populations without cancer and have been pilot tested in patients with cancer.[10-12] We conducted an RCT evaluating the efficacy of Insight compared with standard care in cancer survivors self-reporting cognitive symptoms after completion of curative chemotherapy for a primary solid malignancy.

PATIENTS AND METHODS

This pragmatic longitudinal RCT was conducted at 18 Australian sites. Participants were also able to self-refer via two national breast cancer organizations. Institutional ethics approval was obtained at all sites, and written informed consent was obtained from participants.

Eligible participants were ≥ 18 years old with any solid primary tumor (excluding central nervous system malignancies), who had received definitive treatment of their primary malignancy, including three or more cycles of chemotherapy completed within the previous 6 to 60 months. Participants had to self-report cognitive impairment, indicated by changes in concentration and/or memory, on the two-item European Organization for Research and Treatment of Cancer QLQ-C30 Cognitive Functioning scale.[13] To meet the eligibility criteria, participants had to rate their cognitive complaints as "quite a bit" or greater in one or both domains. Adjuvant endocrine treatments for patients with breast cancer were permitted, but radiotherapy and targeted therapies had to be completed ≥ 12 weeks before study entry. Participants required written English fluency to the equivalent of year 8 education. Access to computer and Internet facilities was mandated.

Participants with evidence of local recurrence or metastatic disease or who had had prior malignancy within the previous 5 years (with the exception of nonmelanomatous skin cancer, cervical cancer in situ, and the cancer of interest) were excluded. Those with an unstable psychiatric condition or current major cognitive disorder were excluded. Psychotropic medications were permitted if participants were receiving a stable dose.

Participants were randomly assigned (1:1) to the Insight intervention or to a control group. Random assignment was managed centrally, using an interactive voice response system. Treatment allocation was determined by minimization. Stratification was for primary tumor type, and in patients with breast cancer, hormonal therapy use.

Telephone Consultation

Before random assignment, all participants participated in a 30-minute structured telephone consultation outlining cognitive compensatory strategies. Standardized scripts were developed outlining cognitive training strategies in four areas: general cognition, memory, concentration, and multitasking. Printed copies of all scripts were mailed to participants.

Intervention Group

Insight from Posit Science is a computerized neurocognitive learning program that is based on the neuroplasticity model. It uses adaptive exercises targeting processing systems aimed at improving cognition through speed and accuracy of information processing.[14] It targets cognitive domains including visual precision, divided attention, working memory, field of view, and visual processing speed, which are frequently affected in patients with cancer.[14,15] The program was provided in compact disc format. Recommended training time was four 40-minute sessions/week for 15 weeks, for a total of 40 hours. The program had a built-in measure of compliance.

Control Group

Participants in the control group received standard care as per their treating physician.

Assessments

Assessments were completed at home at baseline (T1), after the 15-week intervention (T2), and 6 months later (T3). Patient-reported outcome (PRO) questionnaires were mailed to participants. Neuropsychological test files were returned via e-mail.

Measures and Evaluations

The primary outcome was self-reported cognitive function as assessed by the Functional Assessment of Cancer Therapy Cognitive Function version 3 (FACT-COG) questionnaire. The 37-item FACT-COG has acceptable reliability and validity and has been used widely in cancer populations.[16] It comprises four subscales: perceived cognitive impairments (PCI), perceived cognitive abilities, impact of PCI on QOL, and comments from others on cognitive function. The primary outcome score was the FACT-COG PCI score at T2.

The main secondary outcome was objective neuropsychological function as assessed by Cogstate, an 18-minute computerized battery comprising seven tests evaluating processing speed, decision making, working memory, executive function, continuous performance, matching, and new learning.[17] Cogstate was selected because it evaluates multiple domains and can be completed independently at home. It has been validated against extensive neuropsychological tests in longitudinal studies, with good reliability.[18] A total score was derived by standardizing each of the z scores with a mean of 0 and a standard deviation of 1.

Other secondary outcomes included anxiety/depression (12-item General Health Questionnaire), QOL (FACT-General), fatigue (FACT-Fatigue subscale), and stress (14-item Perceived Stress Scale).

All questionnaires have been validated in cancer populations.[19-22]

Statistical Analysis

Linear mixed models with fixed effects of baseline outcome measurement (analysis of covariance), time (categorical), intervention arm, time, arm × time, and stratification and a random effect of participant were used to model each continuous outcome.[23] Tests of treatment effect were undertaken within these models using contrasts, which estimated the difference between the groups at each postbaseline time point, with CIs. The original stratification was based on primary tumor type, and hormonal therapy use in patients with breast cancer, resulting in five strata. Because of limited numbers in some strata, we reduced the strata to three: breast cancer with hormone therapy, breast cancer without hormone therapy, and other cancers. To investigate the sensitivity of results to missing data, we (1) performed multiple imputation for the primary outcome, and (2) fit an adjusted model using baseline variables found to be associated with missing data or the primary outcome.

Statistical significance was set at .05 for the primary outcome of PCI. All other outcomes were considered significant at .01, to informally account for multiple comparisons. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Sample size calculations were based on the comparison of the primary outcome, FACT-COG PCI, between the two groups, at T2. Because there was no available minimal important difference (MID) for this scale, we estimated the value of 6.5 on the basis of the FACT-General MID findings of Webster et al.[24] We assumed a standard deviation of 13, a two-sided *t* test, a type I error of 0.05, 90% power, and equal group sizes. This is just under 10% of the range, a commonly used rule of thumb for MIDs. Assuming 30% attrition, the final sample size was 216.

RESULTS

Between November 2009 and March 2014, 386 participants were assessed for study eligibility. Of these, 242 participants were randomly assigned: 121 to the intervention, Insight, and 121 to the control group (Fig 1). At T2, primary outcome data were available for 192 (79%): 94 in the intervention group (78%) and 98 control subjects (81%). At T3, primary outcome data were available for 184 (76%): 95 in the intervention (79%) and 89 control subjects (74%). These rates were not statistically different ($P = .87$).

Baseline characteristics were well balanced between the groups (Table 1). Median age was 53 years (23 to 74 years); 230 (95%) were female; 216 (89%) had breast cancer; and 13 (5%) had colorectal cancer. The mean time since completion of chemotherapy was 27 months (6 to 60 months).

At T2, there were statistically significant differences in all FACT-COG subscales in the intervention group compared with the control group (Fig 2). The primary outcome of difference between the groups on the FACT-COG PCI was statistically significant, with less PCI in the intervention group at T2 (−7.47; 95% CI, −10.80 to −4.13; $P < .001$). This difference was sustained at T3 (−6.48; 95% CI −9.85 to −3.11; $P = .001$). Perceived cognitive abilities were significantly better in the intervention group at T2 (3.34; 95% CI, 1.98 to 4.70; $P < .001$) and T3 (2.88; 95% CI, 1.50 to 4.25; $P < .001$). Participants in the intervention group reported less impact on their QOL from PCI at T2 (−1.20; 95% CI, −2.20 to −0.20; $P = .02$) and T3 (−1.0; 95% CI, −2.10 to 0.01; $P = .06$). Participants in the intervention group reported fewer comments from others suggesting that they had cognitive impairment at T2 (−0.71; 95% CI, −1.40 to −0.02; $P = .04$), but there were no differences between the groups at T3 (−0.38; 95% CI, −1.08 to 0.33; $P = .29$).

The major secondary outcome was neuropsychological function, and at T2 and T3, there were no significant differences between the groups in total score or in the six cognitive domains

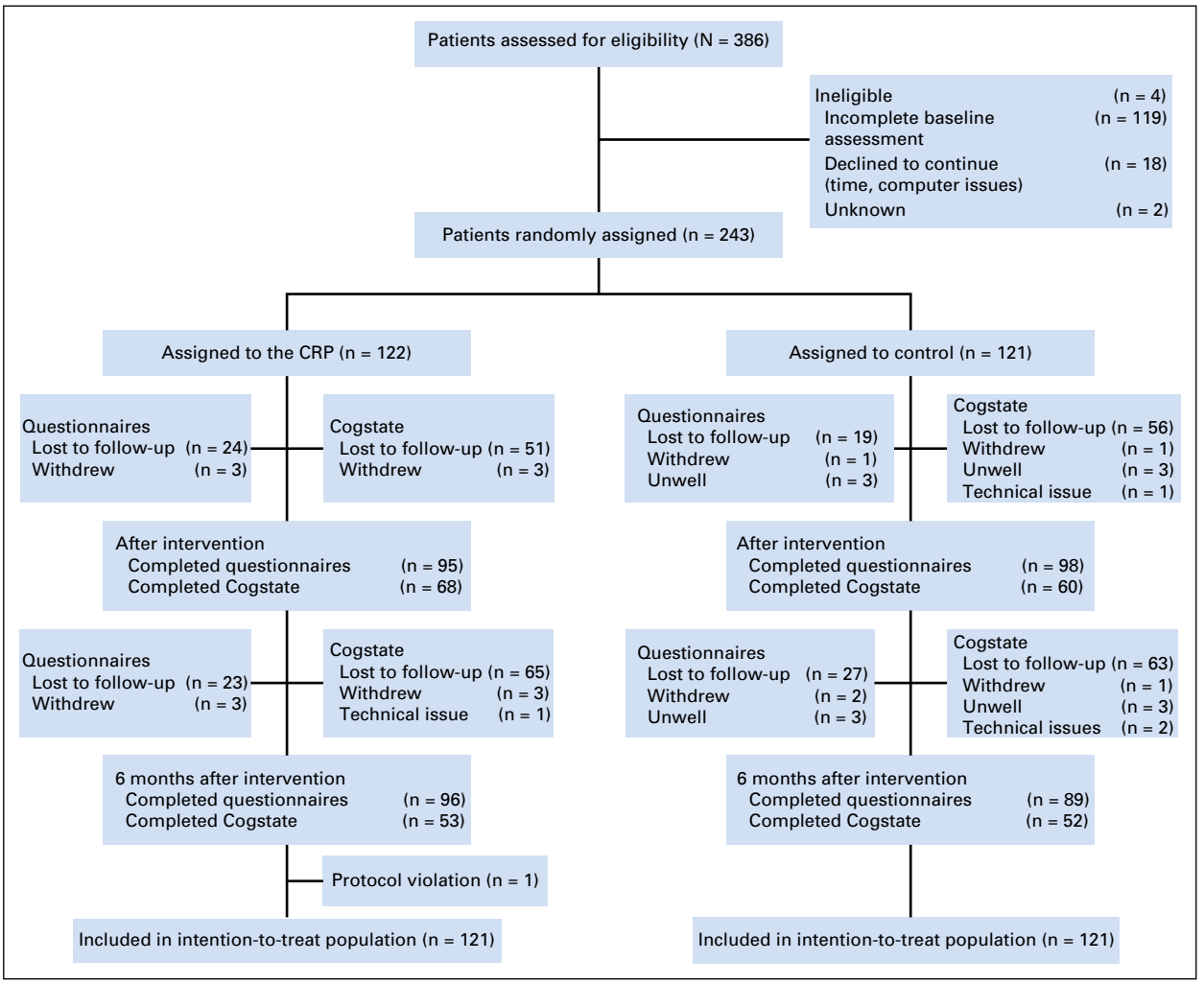

Fig 1. CONSORT diagram. CRP, cognitive rehabilitation program.

Table 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	CRP (n = 121), No. (%)	Control (n = 121), No. (%)
Sex		
Female	116 (96)	114 (94)
Male	5 (4)	7 (6)
Age, years, median (range)	52 (23-74)	54 (31-74)
Married/de facto relationship		
Yes	95 (79)	97 (80)
No	17 (14)	16 (13)
Unknown	9 (7)	8 (7)
Education, years, median (range)	14 (8-19)	12 (3-19)
English as first language		
Yes	117 (97)	117 (97)
No	4 (3)	4 (3)
Smoking history		
Never	72 (60)	63 (52)
Previous	47 (39)	51 (42)
Current	2 (2)	6 (5)
Unknown	0 (0)	1 (1)
Primary tumor type		
Breast	108 (89)	108 (89)
Colorectal	6 (5)	7 (6)
Gynecologic	2 (2)	3 (2)
Lymphoma	2 (2)	1 (1)
Thoracic	2 (2)	1 (1)
Upper GI	0 (0)	1 (1)
Other	1 (1)	0 (0)
Time since completion of chemotherapy, months, mean (range)	27 (6-57)	27 (6-60)
Radiotherapy		
Yes	86 (71)	78 (64)
No	35 (29)	43 (36)
Immune therapy		
Yes	30 (25)	24 (20)
No	91 (75)	97 (80)
Hormone therapy		
Tamoxifen	34 (28)	36 (30)
Letrozole	15 (12)	18 (15)
Anastrazole	29 (24)	25 (21)
Other	6 (5)	6 (5)
None	37 (31)	36 (30)
Previous neurologic history*		
Yes	20 (17)	30 (25)
No	101 (83)	91 (75)
Ever used antidepressants		
Yes	54 (45)	54 (45)
No	67 (55)	67 (55)
Current use of antidepressants		
Yes	28 (23)	25 (21)
No	93 (77)	96 (79)
Patient-reported outcomes, mean (SD)		
Perceived cognitive impairments (FACT-COG PCI)	38.6 (14.3)	41.9 (15.1)
Perceived cognitive abilities (FACT-COG PCA)	12.0 (5.0)	12.5 (5.6)
Comments from others (FACT-COG comments)	3.0 (3.6)	3.3 (3.7)
Cognitive quality of life (FACT-COG QOL)	7.5 (4.2)	7.7 (4.4)
Fatigue (FACT-F)	31.4 (11.5)	32.9 (10.9)
Quality of life (FACT-G)	76.5 (15.3)	77.1 (14.1)
Anxiety and depression (GHQ)	26.9 (5.8)	26.9 (6.0)
Stress (PSS)	25.2 (5.0)	24.5 (4.8)

Abbreviations: CRP, cognitive rehabilitation program; FACT-COG, Functional Assessment of Cancer Therapy Cognitive Function; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; GHQ, General Health Questionnaire; PCA, perceived cognitive abilities; PCI, perceived cognitive impairments; PSS, Perceived Stress Scale; QOL, quality of life; SD, standard deviation.

*Defined as held back a grade in school; required remedial help at school; diagnosed with a learning disability; head injury with loss of consciousness with residual sequelae; history of seizures, dementia, coma, epilepsy, cardiac arrest requiring cardiopulmonary resuscitation; stroke; history of other neurologic risk; history of significant alcohol abuse.

(Table 2). This finding should be interpreted with caution because of missing data rates at both time points. On review of PRO data, we found significant benefits favoring the intervention at T2 in all secondary outcomes, with the exception of QOL (Fig 3). There were lower levels of anxiety/depression in the intervention group at T2 (−1.78; 95% CI, −3.29 to −0.27; $P = .02$), with no significant difference at T3 (−1.50; 95% CI, −3.04 to 0.04; $P = .06$). Similarly, there were lower levels of fatigue in the intervention group at T2

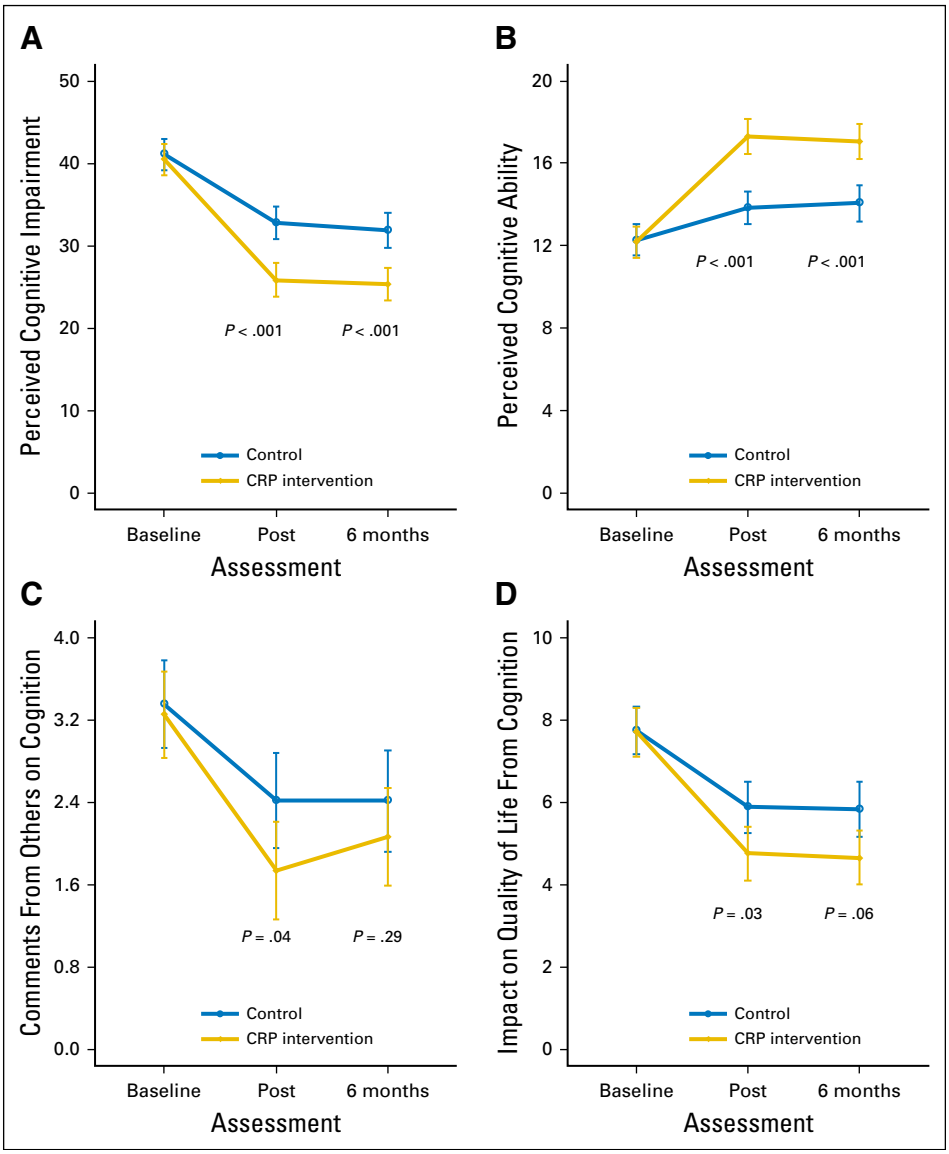

Fig 2. Mean scores for self-reported cognitive function over time, by group. CRP, cognitive rehabilitation program.

(2.44; 95% CI, 0.25 to 4.62; $P = .03$), with no significant difference at T3 (2.16; 95% CI, −0.05 to 4.37; $P = .06$). There was no difference in global QOL between the groups at T2 (1.66; 95% CI, −0.93 to 4.24; $P = .21$), but the intervention group had better global QOL at T3 (3.39; 95% CI, 0.77 to 6.01; $P = .01$). There were benefits in perceived stress in the intervention group at T2 (−1.30; 95% CI, −2.48 to −0.12; $P = .03$) and T3 (−1.85; 95% CI, −3.05 to −0.65; $P = .01$). Figure 4 illustrates the PRO as standardized effect sizes with 95% CIs. It confirms a clear direction of benefit for the intervention at T2 and T3, with T2 standardized effect sizes of 0.28 for FACT-COG PCI and 0.31 for perceived cognitive abilities.

The sensitivity analysis results (Appendix, online only) were similar to the primary analysis, in both the magnitude of the estimates and the statistical significance, indicating that data were likely to not be informatively missing. Participants who did not complete the T2 assessment had higher rates of antidepressant use and were younger.

Of those randomly assigned to the intervention, 104 (86%) used the program, and 14% never started it. The average total training time was 25.08 hours (0.19 to 55.82 hours) of a recommended 40 hours. Only 33 participants (27%) completed the program in the recommended 15-week timeframe. Using regression models, we performed exploratory dose-response analyses for intervention training time with both change in FACT-COG PCI and Cogstate total score. There was no evidence of dose-response for either outcome. Further exploratory analyses compared the FACT-COG PCI change from baseline to T2 for those above and below the mean training time (25.08 hours). Those who trained for $>$ 25.08 hours had a change of 16.3 points, compared with 12.6 points for those who trained for $<$ 25.08 hours (difference, 3.7; 95% CI, −1.9 to 9.2). We used regression models to explore the factors associated with training time and found that higher baseline anxiety/depression was marginally associated with less training time ($P = .03$). There was no evidence of association for other baseline variables including fatigue, PCI, and Cogstate score.

Table 2. Objective Neuropsychological Test Results (Cogstate)

Cognitive Domain Assessed	Task Name	Primary Outcome Measure	Timing of Assessment	CRP (n = 121)	Control (n = 121)	Difference (95% CI)	*P*
Visual episodic memory	Continuous paired associate learning task	Total errors*	T1	28.04	27.04	—	—
			T2	33.80	28.23	5.56 (−1.26 to 12.38)	.11
			T3	25.87	27.09	−1.22 (−8.88 to 6.45)	.76
Problem solving and reasoning	Groton maze learning task	Total errors†	T1	46.06	45.82	—	—
			T2	43.47	44.51	−1.04 (−5.03 to 2.96)	.61
			T3	41.95	45.30	−3.36 (−7.86 to 1.15)	.14
Visual learning and memory	One card learning	Arcsine proportion correct‡	T1	1.00	1.03	—	—
			T2	1.05	1.00	0.05 (−0.01 to 0.11)	.08
			T3	1.05	0.98	0.06 (−0.00 to 0.13)	.06
Working memory consolidation	One back task	Speed (log_{10} milliseconds)§	T1	2.89	2.90	—	—
			T2	2.89	2.90	−0.00 (−0.03 to 0.02)	.71
			T3	2.87	2.90	−0.03 (−0.05 to −0.00)	.05
Working memory consolidation	Two back task	Speed (log_{10} milliseconds)§	T1	2.95	2.96	—	—
			T2	2.98	2.97	0.01 (−0.02 to 0.04)	.64
			T3	2.97	2.96	0.01 (−0.02 to 0.04)	.48
Information processing/psychomotor function	Detection task	Speed (log_{10} milliseconds)§	T1	2.56	2.57	—	—
			T2	2.55	2.57	−0.02 (−0.05 to 0.02)	.33
			T3	2.56	2.58	−0.02 (−0.06 to 0.02)	.27
Attention	Identification task	Speed (log_{10} milliseconds)§	T1	2.73	2.74	—	—
			T2	2.73	2.72	0.00 (−0.01 to 0.02)	.60
			T3	2.72	2.74	−0.02 (−0.04 to −0.00)	.04
Total score			T1	−0.03	0.05	—	—
			T2	0.09	0.03	0.00 (−0.07 to 0.07)	.21
			T3	0.00	0.06	−0.02 (−0.06 to −0.22)	.09

Abbreviations: CRP, cognitive rehabilitation program; T1, baseline; T2; after intervention; T3, 6 months after intervention.
*Number of errors made in correctly placing each of the four patterns in their location four times (lower score = better performance).
†Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session (lower score = better performance).
‡Accuracy of performance. Arcsine transformation of the square root of the proportion of correct responses (higher score = better performance).
§Speed of performance. Mean of the log_{10} transformed reaction times for correct responses (lower score = better performance).

DISCUSSION

This was a large, longitudinal, RCT evaluating a Web-based cognitive rehabilitation program in patients with cancer reporting cognitive symptoms after chemotherapy. Those randomly assigned to the intervention had improved perceived cognitive function after the intervention that was sustained at 6 months. There were no major differences in objective neuropsychological test results between the groups. Importantly, symptoms of anxiety/depression, fatigue, and stress were lower in the intervention group on completion of the program, and QOL was improved at 6 months.

To our knowledge, this is the largest RCT to evaluate a cognitive rehabilitation program in patients with cancer. There have been a number of small wait-list control trials of cognitive interventions, predominantly in patients with breast cancer.[8,9,25-27] These studies have been heterogeneous, with differing primary outcomes and diverse cognitive training strategies.

Von Ah et al[25] conducted a three-arm, single-blind RCT of training in memory and processing speed in 82 breast cancer survivors 6 years after treatment. The groups included group sessions of memory training, the Insight program, and a wait-list group. They found that training of memory and processing speed improved objective cognitive performance. There were also significant improvements in perceived cognitive function, mood, anxiety, fatigue, and QOL in the cognitive training groups compared with the wait-list control group.

Cherrier et al[28] conducted an RCT of a 7-week cognitive rehabilitation intervention in 28 participants with various tumor types, a median of 3 years after treatment. The intervention comprised group sessions including content on memory aids, development of memory skills, and mindfulness meditation. The intervention group had improvements in PCI and ability, less impact of their cognitive symptoms on QOL, and improvements on objective measures of attention.

The major strengths of our study are the RCT design, the large sample size, and assessment of both self-reported and neuropsychological function, both of which are important to cancer survivors and are valid end points. The pragmatic design, with broad eligibility criteria incorporating both sexes, no upper age limit, and patients with any primary solid tumor type, is a strength. The rationale was to ensure that the results were generalizable to the majority of cancer survivors as recommended by the International Cognition and Cancer Task Force.[29,30] The selection of a home-based intervention and remote assessments was to ensure equity of access to cancer survivors throughout Australia, irrespective of geographical location.

Despite our broad selection criteria, the majority of study participants were patients with breast cancer; this was driven by patient interest and recruitment strategies. The number of participants with other primary tumor types was too small for subgroup analysis. However, there is no inherent mechanism suggesting that this intervention would not yield similar results for other tumor types.

This study has a number of limitations. We acknowledge that the ideal study design would have included a third group randomly

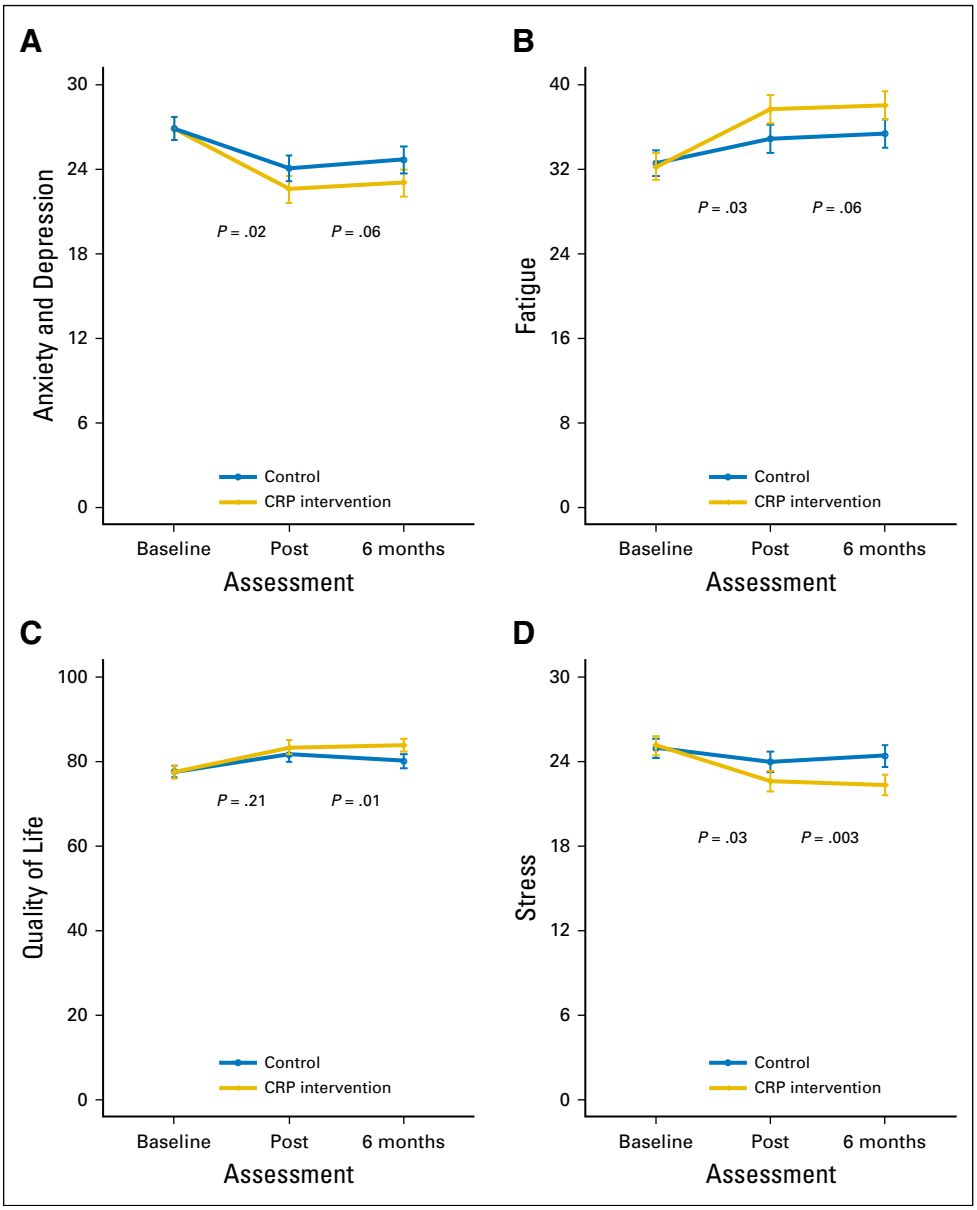

Fig 3. Mean scores for patient-reported outcomes over time, by group. CRP, cognitive rehabilitation program.

assigned to a 40-hour nontherapeutic intervention. This was not feasible because of difficulties in ensuring that the intervention would be nontherapeutic, home based, and acceptable to participants and for budgetary and resource considerations. It is possible that simply performing an intervention, or expectation of benefit, may improve self-reported cognitive impairment, but any placebo effect derived on completion of the intervention is likely to diminish over time and to not be sustained at T3. We attempted to control for placebo effect with the telephone consultations with both groups. Although all participants took part in the telephone consultations, differences were seen favoring the intervention group, suggesting a benefit from the program, beyond that of the telephone consultation alone.

Another limitation of the study was inherent in the pragmatic study design. Participants were unsupervised when performing the intervention, and assessments were completed remotely. This had a significant impact on completion rates, particularly for the neuropsychological assessment with Cogstate. This was challenging for several participants because of the required level of computer literacy to install and later reaccess Cogstate. Similarly, some participants experienced technical difficulties using Insight, and with no in-person information technology support available, in some instances these issues were unable to be rectified. This had implications for the use of Insight and the median training time. Reassuringly, the study met its primary end point, with an average training time of 25 hours, rather than the recommended 40-hour training period. With Insight moving to an online platform, this is less likely to be problematic in the future and will enhance translation into practice. Taken together, these issues resulted in missing data. We performed additional statistical analyses to investigate this further (Appendix).

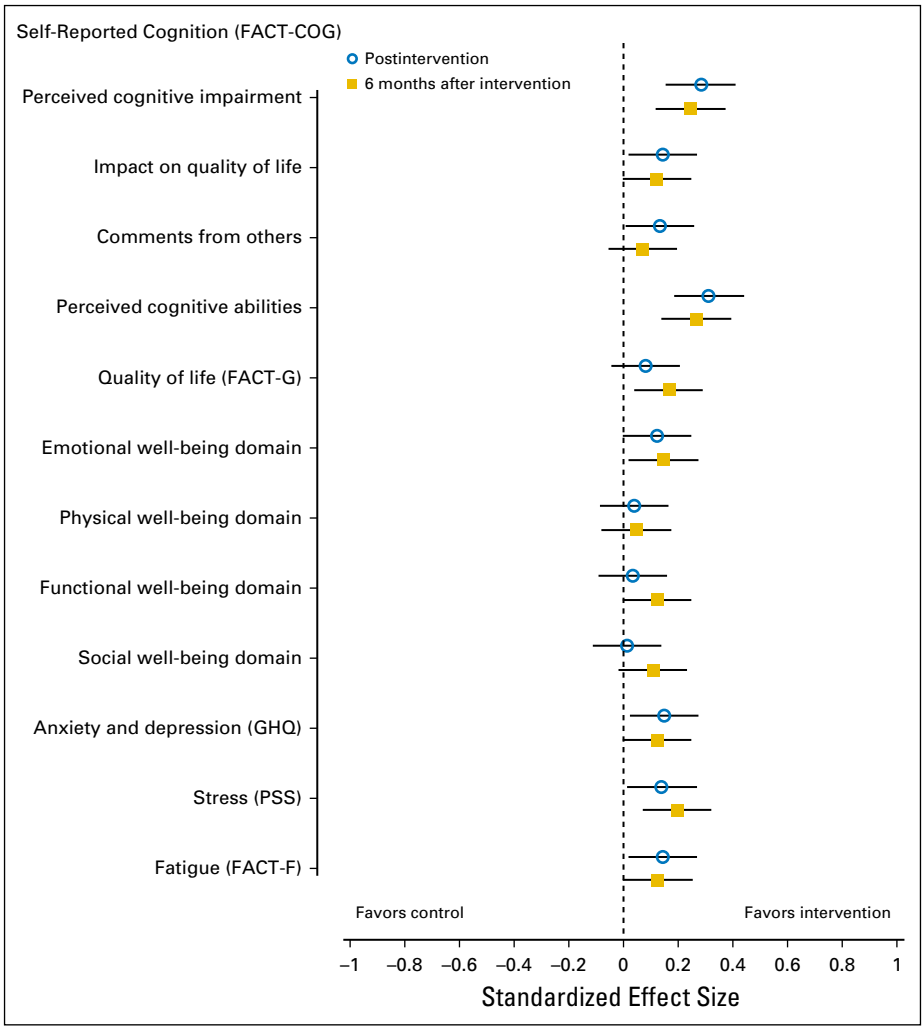

Fig 4. Standardized effect sizes (and 95% CIs) of the difference between treatment groups in patient-reported outcomes. Standardized effect sizes < 0.2 are not likely to be clinically important. FACT-COG, Functional Assessment of Cancer Therapy Cognitive Function; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; GHQ, General Health Questionnaire; PSS, Perceived Stress Scale.

We found no evidence of a difference in objective neuropsychological results between the groups. One could question whether a difference would have been seen with higher completion rates for neuropsychological testing and if participants had completed the recommended 40-hour training period. However, previous studies have shown a weak association between cognitive symptoms and objective cognitive function. It is possible that different constructs were measured, that the Cogstate battery did not have the sensitivity required to detect the subtle cognitive impairment that cancer survivors typically experience, or that the ideal conditions under which formal neuropsychological testing is performed may not reproduce a cancer survivor's cognitive symptoms.

In line with the findings of previous studies, our results show that self-reported cognitive impairment is associated with increased anxiety/depression and fatigue and poorer QOL. However, the relationship is complex. We do not believe that cognitive symptoms can be explained fully by affective symptoms, because we found sustained improvements in cognitive symptoms in the intervention group at 6 months. We acknowledge that some of the improvements in PRO in the intervention group may have been a result of participants' self-efficacy or an expectancy effect engendered by performing an activity to address their symptoms.

The study collected data on a number of PRO, with multiple tests undertaken at different time points. We acknowledge that some of the trends seen, particularly in the individual cognitive domains of Cogstate and in QOL domains, may be chance findings.

To date, there has been a large unmet need for effective treatment options for cancer survivors experiencing cognitive symptoms after chemotherapy treatment. Previous research has shown cognitive rehabilitation strategies to be feasible, with preliminary evidence of efficacy. Our large RCT adds weight to this evidence, confirming that the use of Insight led to an improvement in cognitive symptoms. Importantly, there were also improvements in PRO, including QOL and reduction in stress, fatigue, and anxiety/depression. The program has the additional advantages of being relatively inexpensive and home based, allowing individuals to direct their own treatment. The program has the potential to provide a new treatment option for patients with cancer with cognitive symptoms, where previously none existed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Appendix

Missing Data Investigation

We compared baseline characteristics between participants who were missing and those who were observed after the intervention (T2) for the primary outcome, self-reported cognitive function, measured by the Functional Assessment of Cancer Therapy Cognitive Function (FACT-COG) perceived cognitive impairment (PCI) subscale, and objective neuropsychological function assessed by Cogstate. We used *t* tests to compare continuous variables, including age, years of education, and time since completion of chemotherapy. We used χ^2 tests to compare categorical variables, including married/de facto relationship, smoking history (PCI only), radiotherapy, immune therapy, hormone therapy (yes/no), previous neurologic history, previous use of antidepressants, and current use of antidepressants. We used Fisher's exact test to compare categorical variables with small expected cell frequencies, including sex, English as first language, smoking history (Cogstate only), primary tumor type, and hormone therapy.

Participants who had missing PCI at T2 were younger (49 *v* 54 years old, $P = .001$) and had a higher proportion of previous (26% *v* 19%, $P = .01$) and current (34% *v* 19%, $P = .02$) antidepressant use compared with those who were observed (Table A1). Participants who had missing Cogstate at T2 had fewer years of education (13 *v* 14 years, $P = .01$) and a higher proportion of previous (56% *v* 35%, $P = .0008$) and current (31% *v* 14%, $P = .002$) antidepressant use compared with those who were observed (Table A2).

Sensitivity Analysis for Missing Data: Multiple Imputation and Adjusted Model

As a sensitivity analysis for missing data, we performed multiple imputation (MI) for the primary outcome, self-reported cognitive function, measured by the FACT-COG PCI subscale. MI reflects uncertainty in predictions of missing data by drawing a set of values, as opposed to a single value, from a predictive distribution for each missing observation. Analysis is performed on each data set, and the results are combined using Rubin's rules (Rubin DB: Multiple imputation for nonresponse in surveys. John Wiley & Sons, 2004).

Table A3 displays the amount of missing outcome data by treatment arm and follow-up. All patients had complete PCI data at baseline. After the intervention, 23 participants in the control arm (19%) and 27 in the intervention arm (22%) had missing PCI data. At 6 months after the intervention, 32 in the control arm (26%) and 26 in the intervention arm (21%) had missing PCI data.

Imputation was performed in wide form, with a single data row for each participant, so that correlation within participant was maintained. For the imputation model, we used arm (intervention, control), stratification (five strata on the basis of primary tumor type and use/nonuse of hormonal therapies for patients with breast cancer), and other patient-reported outcomes collected during the trial, including each of the FACT-COG subscales (impact on quality of life, comments from others, perceived cognitive abilities), the Functional Assessment of Cancer Therapy-General total score, Functional Assessment of Cancer Therapy-Fatigue subscale, General Health Questionnaire, and Perceived Stress Scale to help predict values for the missing PCI data. We also considered covariates thought to be associated with missing data and the outcome using logistic regression and mixed models, respectively. The covariates considered were age, antidepressant use (ever or current), smoking history (never, previous, current), tumor stage (1 to 3), previous cognitive problems (yes, no), number of chemotherapy cycles (continuous), and time since last chemotherapy (continuous). A participant was considered to have previous cognitive problems if he or she indicated at least one of the following: being held back a year in school, remedial help required at school, a learning disability diagnosis, head injury with loss of

consciousness, residual sequalae such as headaches or blurred vision, seizures, epilepsy, dementia, cardiac arrest requiring cardiopulmonary resuscitation, coma, stroke, history of other neurologic risk, or history of significant alcohol abuse. Of the covariates, only age, antidepressant use, and tumor stage were found to be associated with the outcome. Tumor stage was associated with missing data but led to convergence issues during the imputation procedure; therefore, age and antidepressant use, together with the aforementioned variables, were used in the imputation models.

We used the MI procedure in SAS statistical software version 9.4 (SAS Institute, Cary, NC). We used the Markov chain Monte Carlo method, which assumes that the data have a multivariate normal distribution and completes 200 burn-in iterations before the first imputation and 100 iterations between imputations. We imputed all missing values and used a single chain to produce 20 imputations. All imputed values were rounded to the nearest whole number and were constrained to each variable's possible range. MIs were performed by treatment arm. Using the completed data set, we analyzed PCI using linear mixed models adjusting for baseline PCI and stratification. After the intervention and at follow-up, the overall difference (and 95% CIs) between treatment arms and means for each treatment arm and time point were calculated using Rubin's rules as the average of estimates from each of the 20 MI data sets.

We also fitted an adjusted model, using our primary model, as well as several baseline variables including age, antidepressant use, education, months since chemotherapy, previous cognitive problems, baseline stress, and baseline fatigue.

Our analysis using MI yielded results similar to those of the primary analysis (Table A4). When MI was used, a slightly smaller difference between treatment arms was seen after the intervention (difference, -7.0; 95% CI, -10.2 to -3.9; $P < .001$) and 6 months after the intervention (difference, -6.4; 95% CI, -9.8 to -3.1; $P < .001$). The adjusted model also gave similar results, although they were slightly stronger.

Table A1. Baseline Characteristics of Participants With Observed and Missing PCI at T2

Characteristic	Observed (n = 192), No. (%)	Missing (n = 50), No. (%)	*P*
Sex			
Female	182 (95)	48 (96)	.73
Male	10 (5)	2 (4)	
Age, years, median (range)	54 (31-74)	49 (23-72)	.001
Married/de facto relationship			
Yes	153 (80)	39 (78)	.91
No	16 (9)	7 (14)	
Unknown	13 (7)	4 (8)	
Education, years, median (range)	14 (3-19)	13 (9-19)	.43
English as first language			
Yes	187 (97)	47 (94)	.37
No	5 (3)	3 (6)	
Smoking history			
Never	110 (57)	25 (50)	.46
Previous	74 (39)	74 (24)	
Current	7 (4)	1 (2)	
Unknown	1 (1)	0 (0)	
Primary tumor type			
Breast	172 (90)	44 (88)	.21
Colorectal	12 (6)	1 (2)	
Gynecologic	3 (2)	2 (4)	
Lymphoma	2 (1)	1 (2)	
Thoracic	2 (1)	1 (2)	
Upper GI	1 (1)	0 (0)	
Other	0 (0)	1 (2)	
Time since completion of chemotherapy, months, mean (range)	26 (6-60)	30 (8-51)	.08
Radiotherapy			
Yes	128 (67)	36 (72)	.47
No	64 (33)	14 (28)	
Immune therapy			
Yes	40 (21)	14 (28)	.28
No	152 (79)	36 (72)	
Hormone therapy			
No	56 (29)	17 (34)	
Yes	136 (71)	33 (66)	.51
Tamoxifen	56 (29)	14 (28)	.06
Letrozole	24 (13)	9 (18)	
Anastrazole	49 (26)	5 (10)	
Other	7 (4)	5 (10)	
Previous neurologic history*			
Yes	37 (41)	30 (60)	.30
No	114 (59)	20 (40)	
Ever used antidepressants			
Yes	78 (19)	13 (26)	.01
No	155 (81)	37 (74)	
Current use of antidepressants			
Yes	36 (19)	17 (34)	.02
No	156 (81)	33 (66)	
Patient-reported outcomes, mean (SD)			
Perceived cognitive impairments (FACT-COG PCI)	39.9 (15.1)	41.5 (13.4)	.46
Perceived cognitive abilities (FACT-COG PCA)	12.3 (5.0)	11.8 (6.4)	.61
Comments from others (FACT-COG comments)	3.3 (3.9)	2.7 (2.9)	.24
Cognitive quality of life (FACT-COG QOL)	7.3 (4.2)	8.7 (4.8)	.06
Fatigue (FACT-F)	33.1 (10.8)	28.4 (12.1)	.02
Quality of life (FACT-G)	78.0 (14.0)	72.4 (16.4)	.03
Anxiety and depression (GHQ)	26.5 (5.9)	28.2 (5.6)	.07
Stress (PSS)	24.4 (4.9)	26.4 (4.9)	.01

Abbreviations: CRP, cognitive rehabilitation program; FACT-COG, Functional Assessment of Cancer Therapy Cognitive Function; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; GHQ, General Health Questionnaire; PCA, perceived cognitive ability; PCI, perceived cognitive impairment; PSS, Perceived Stress Scale; QOL, quality of life; T2, after intervention.

*Defined as held back a grade in school; required remedial help at school; diagnosed with a learning disability; head injury with loss of consciousness with residual sequelae; history of seizures, dementia, coma, epilepsy, cardiac arrest requiring cardiopulmonary resuscitation, stroke; history of other neurologic risk; history of significant alcohol abuse.

Table A2. Baseline Characteristics of Participants With Observed and Missing Cogstate at T2

Characteristic	Observed (n = 132), No. (%)	Missing (n = 110), No. (%)	*P*
Sex			
Female	126 (95)	104 (95)	.77
Male	6 (5)	6 (5)	
Age, years, median (range)	54 (31-74)	52 (23-74)	.08
Married/de facto relationship			
Yes	105 (80)	87 (79)	.34
No	21 (16)	12 (11)	
Unknown	6 (5)	11 (10)	
Education, years, median (range)	14 (8-19)	13 (3-19)	.01
English as first language			
Yes	129 (98)	105 (95)	.47
No	3 (2)	5 (5)	
Smoking history			
Never	74 (56)	61 (56)	.94
Previous	53 (40)	45 (41)	
Current	5 (4)	3 (3)	
Unknown	0 (0)	1 (1)	
Primary tumor type			
Breast	119 (90)	97 (88)	.53
Colorectal	8 (6)	5 (5)	
Gynecologic	1 (1)	5 (4)	
Lymphoma	2 (2)	1 (1)	
Thoracic	1 (1)	2 (2)	
Upper GI	1 (1)	0 (0)	
Other	0 (0)	1 (1)	
Time since completion of chemotherapy, months, mean (range)	25 (6-56)	28 (7-60)	.06
Radiotherapy			
Yes	91 (69)	73 (66)	.67
No	41 (31)	37 (34)	
Immune therapy			
Yes	29 (22)	25 (23)	.89
No	103 (78)	85 (77)	
Hormone therapy			
No	36 (27)	37 (34)	
Yes	96 (73)	73 (66)	.29
Tamoxifen	39 (30)	31 (28)	.40
Letrozole	16 (12)	17 (16)	
Anastrazole	35 (27)	19 (17)	
Other	6 (5)	6 (6)	
Previous neurologic history*			
Yes	24 (18)	26 (24)	.30
No	108 (82)	84 (76)	
Ever used antidepressants			
Yes	46 (35)	62 (56)	.0008
No	86 (65)	48 (44)	
Current use of antidepressants			
Yes	19 (14)	34 (31)	.002
No	113 (86)	76 (69)	
Patient-reported outcomes, mean (SD)			
Perceived cognitive impairments (FACT-COG PCI)	39.6 (14.8)	41.0 (14.8)	.44
Perceived cognitive abilities (FACT-COG PCA)	12.2 (4.6)	12.2 (6.1)	.95
Comments from others (FACT-COG comments)	3.17 (3.7)	3.15 (3.7)	.95
Cognitive quality of life (FACT-COG QOL)	7.17 (4.1)	8.18 (4.6)	.07
Fatigue (FACT-F)	33.4 (10.2)	30.6 (12.2)	.06
Quality of life (FACT-G)	78.1 (12.8)	75.3 (12.2)	.15
Anxiety and depression (GHQ)	26.4 (5.7)	27.5 (6.0)	.15
Stress (PSS)	24.7 (4.8)	25.0 (5.1)	.55

Abbreviations: CRP, cognitive rehabilitation program; FACT-COG, Functional Assessment of Cancer Therapy Cognitive Function; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; GHQ, General Health Questionnaire; PCS, perceived cognitive abilities; PCI, perceived cognitive impairment; PSS, Perceived Stress Scale; QOL, quality of life; T2, after intervention.

*Defined as held back a grade in school; required remedial help at school; diagnosed with a learning disability; head injury with loss of consciousness with residual sequelae; history of seizures, dementia, coma, epilepsy, cardiac arrest requiring cardiopulmonary resuscitation, stroke; history of other neurologic risk; history of significant alcohol abuse.

Table A3. Missing Data of Perceived Cognitive Impairments by Treatment Arm and Time

Time of Assessment	CRP (n = 121), No. (%)	Control (n = 121), No. (%)
T1	0 (0)	0 (0)
T2	27 (22)	23 (19)
T3	26 (21)	32 (26)

Abbreviations: CRP, cognitive rehabilitation program; T1, baseline; T2, after intervention; T3, 6 months after intervention.

Table A4. Perceived Cognitive Impairments From the Primary Analysis and Multiple Imputation

Analysis/Time of Assessment	CRP	Control	Difference (95% CI)	*P*
Primary analysis				
T1	39.6	42.9	—	—
T2	26.0	33.5	−7.5 (−10.8 to −4.1)	< .001
T3	25.8	32.3	−6.5 (−9.9 to −3.1)	< .001
Multiple imputation				
T1	40.4	41.2	—	—
T2	26.1	33.1	−7.0 (−10.2 to −3.9)	< .001
T3	26.5	32.0	−6.4 (−9.8 to −3.1)	< .001
Adjusted model				
T1	40.5	41.4	—	—
T2	25.5	33.7	−8.2 (−11.7 to −4.7)	< .001
T3	25.3	32.5	−7.2 (−10.7 to −3.7)	< .001

Abbreviations: CRP, cognitive rehabilitation program; T1, baseline; T2, after intervention; T3, 6 months after intervention.